REMARKS

I. Notice of Appeal

Applicants filed a notice of appeal to on July 31, 2003 in connection with the instant application. Applicants herewith submit a Request for Continued Prosecution and understand that the filing of an RCE will be treated as a withdrawal of the Notice of Appeal in accordance with MPEP § 1215.

II. Status of the claims

All the previously pending claims have been cancelled. New claims 108-119 have been added to replace these claims. Claim 108 corresponds to previous claim 106, but contains the proviso that the non-homologously recombinant cells are screened for expression of a desired endogenous gene and that the cell expressing the desired endogenous gene is isolated and cloned prior to being introduced into the animal. Support for both of these steps can be found in original claim 81, steps (d) and (e) and original claim 101. Claims 109-114 correspond to previous claims 83-88, respectively. Claim 115 corresponds to previous claim 92. Claim 116 corresponds to previous claim 100. Claim 117 is supported in original claim 99. Claims 118 and 119 correspond to previous claims 102 and 103, respectively. Accordingly, no new matter has been added with these claims. Applicants reserve the right to file one or more continuation applications directed to the cancelled or deleted subject matter.

III. Examiner Interview

Applicants thank Examiner Ram Shukla for the telephonic interview held on October 21, 2003 with Applicants' attorney Anne Brown. Applicants' attorney discussed the February 14, 2001 Office Action from former Examiner Peter Brunovskis. The discussion focused on the basis for rejection under 35 U.S.C. § 112, first paragraph, non-enablement. The Examiner's fundamental position appeared to be that the specification asserted only one utility for Applicants' cells introduced into animals, i.e., cell therapy, and cell therapy was not enabled. He took the position that there was no non-therapeutic specific, substantial, or credible utility for Applicants' cells in animals. Examiner Shukla agreed that this was Examiner Brunovskis's rationale.

Applicants' attorney then pointed out that Applicants submitted numerous references collectively demonstrating substantial utility for Applicants' cells in animals. The references collectively show that in the art, recombinant cells engineered to express specific desired proteins were introduced into animals to express those proteins in several non-therapeutic contexts. Applicants' attorney explained that Applicants' cells, although made by a different procedure, would substitute for any of the cells in the references. Because Applicants' cells could be reasonably predicted to function in the same way, it was reasonably predictable that they would have the same use. Because the references collectively demonstrate substantial utility and because Applicants' cells could be put to the same use, it was Applicants' position that Applicants' cells in animals also had substantial utility.

Examiner Shukla, however, took the position that Applicants' cells were different from the cells disclosed in the references and, therefore, did not have the same use. He pointed out that the cells in the references expressed specific desired genes. He cited U.S. 5,733,761 as an example. He indicated that a cell expressing a desired gene was introduced into the animal. He then indicated that the Applicants' claimed cells were fundamentally different because it was not known what gene was being expressed when the cell was introduced into an animal. Applicants' attorney pointed out that Applicants' cells could express any desired gene. The Examiner inquired whether the method contained a step for ascertaining whether a particular gene was expressed. The previous claims did not explicitly contain that limitation. Accordingly, Applicants indicated that this limitation would be added to the claims.

IV. The Rejections

A. Rejection of claim 107 under 35 U.S.C. § 112, first paragraph, written description

On page 2 of the Office Action claim 107 remains rejected on the grounds that the specification did not reasonably convey possession of the claimed invention. This rejection is moot in view of Applicants' cancellation of this claim

B. Rejection under 35 U.S.C. § 112, first paragraph, enablement

On page 3 of the Office Action claims 83-88, 92, 100-103, 106 and 107 have been rejected on the grounds that these claims are not enabled "for the reasons of record set forth in

the previous Office Actions of 2/14/01 and 8/23/01 [These are Peter Brunovskis's Office Actions] and as discussed below". Applicants respectfully traverse the rejection.

As indicated above, the grounds for the Brunovskis rejection are as follows: The only utility asserted in the specification for Applicants' cells in animals was cell therapy; cell therapy was not enabled; therefore the claimed invention was not enabled.

Applicants disagreed. They took the position that there was substantial non-therapeutic utility for Applicants' cells in animals. They based this position on the following grounds. Recombinant cells, expressing desired proteins by exogenous coding sequences in expression vectors or by endogenous gene activation through homologous recombination, had substantial, non-therapeutic utility. Applicants' cells were interchangeable for these non-therapeutic uses because Applicants' cells could be selected for over-expression of a desired protein. Therefore, Applicants' cells had the same utility.

Recombinant cells were widely used in the industry for various non-therapeutic purposes. Applicants presented numerous references showing the use of recombinant cells to produce proteins for non-therapeutic purposes in animals. The references collectively demonstrate substantial utility for protein expression in animals by means of introduced recombinant cells. Applicants explained that Applicants' cells, expressing desired endogenous genes, could effectively substitute for any of the recombinant cells used in the art. Therefore, there was substantial utility for Applicants' cells in animals.

This issue has been addressed with Examiner Shukla in the interview. Please see "Examiner Interview" above.

On page 4 of the Office Action dated April 25, 2003, the Examiner responds to Applicants' arguments. Essentially, the Examiner indicates that the Declaration is not persuasive to obviate the rejection because the cells in the references differ from Applicants' cells. This was clarified in the interview. Regarding U.S. 5,641,670 and 5,733,761, the Examiner states "expression of a certain endogenous gene is activated, in contrast to the method of the instant application where expression of any gene is activated and one may or may not produce a full-length protein". Office Action page 5. The Examiner has basically applied this rationale to the rest of the cited references. He then summarizes that "therefore, the utility described for the different types of cells (discussed by the inventor in the declaration) cannot provide readily apparent utility for the cells of the instantly claimed invention."

On page 6 of the Office Action the Examiner also discusses the Applicants' position that the specification teaches the isolation and purification of protein produced in an animal by the cells of the invention. Again, the Examiner takes the position that "the cells used in the claimed invention are not related or similar to any other cells that the Applicants have discussed, the method used in these other unrelated art [sic] cannot be used to support the enablement or other readily apparent utilities."

This point was discussed in the interview. The Examiner's basic point was that the claims, as written, do not disclose expression of specific desired genes in contrast to the references of the claimed invention that do disclose the expression of specific desired genes. Applicants pointed out that when Applicants' cells are found to express a specific desired gene, those cells could be used in the same way that the cells disclosed in the references are used.

The cells disclosed in the references expressed desired genes by a variety of mechanisms. For example, a desired endogenous gene can be activated by homologous recombination (e.g., Treco). Alternatively, a desired gene can be expressed in a cell by an exogenous coding sequence on a viral expression vector (e.g., Shaw). Alternatively, classical expression vectors can be introduced into a cell so that cell is expressing an exogenous coding sequence for a desired gene (e.g., Bronson). Applicants' cells can be used in an equivalent manner. A cell known to express a specific desired gene can be used in the same well-known utilities that are disclosed in the references.

Applicants present claim 108 that recites that a cell expressing a desired endogenous gene is selected and introduced into the animal.

On page 4 of the Office Action the Examiner also asserts that the claim is not enabled because "the only description of an *in vivo* method is usually a single sentence that says that the cells can be used for *in vivo* expression, such as on page 7, line 8-9. ...it is emphasized that the

specification does not teach any specific teaching for carrying out any *in vivo* method. Rather, Applicants have argued for support in the art and that an artisan would be able to do it."

On page 7 of the Office Action the Examiner supports the rejection by supplying a quotation from Genentech v. Novo Nordisk, 42 U.S.P.Q2d 1001 (Fed Cir 1997). The Examiner states that it is often argued that the specification need not disclose what is well-known in the art, citing Hybritech, Inc. v. Monoclonal Antibodies 802 F.2d 1367; 231 U.S.P.Q81 (Fed Cir 1986). But Genentech is applied as follows: "However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; ...It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement".

In Genentech, the claims were broadly directed to a method to express mature human growth hormone with the following steps (1) express a human growth hormone conjugate containing an extra amino acid at the carboxy terminal end which is cleavable by an enzyme and (2) obtain the conjugate protein and cleave it with an enzyme to obtain the mature human growth hormone. In this particular case, the Court stated that there was no description of any specific cleavable conjugate protein and no description of enzymes or other conditions that could be used to cleave such conjugate proteins. The Court stated that the specification merely described how a cleavable fusion might be used and then named one enzyme that might be used as a cleavage agent. The Court stated "Thus, the specification does not describe a specific material to be cleaved or any reaction conditions under which cleavable fusion expression would work".

Accordingly, the case can be distinguished. In Applicants' specification, Applicants have disclosed the starting materials, i.e., cells containing desired activated genes. These cells are then implanted into animals, Methods of implantation would have been well-known and not specific to Applicants' cells. The references disclose various well-known routes of introducing recombinant cells. These include intramuscular, intravenous, and intraperitoneal. These references were published (or, in the case of patent applications, filed) 1984 (Brodeur), 1989 (Kints), 1989 (Stewart), 1997 (Shaw), 1995 (Chen), 1987 (Garver), 1996 (Bronson), 1985 (McNiece), 1991 (Treco) and 1986 (Ishihara). Accordingly, it has been known, in many cases for ten to twenty years, how to introduce cells into an animal and obtain protein expression. There is no reason to believe that Applicants' cells would be a special case. Accordingly, it is reasonably predictable that Applicants' cells could be implanted into an animal to express protein just like the other recombinant cells.

Moreover, there is no reason to believe that a gene that has been activated *in vitro* would be shut off *in vivo*. This is evidenced by the references. These cells are established *in vitro* either using expression vectors containing exogenous coding sequences or by expressing endogenous genes that have been activated *in vitro*. Expression continues to occur when these cells are implanted *in vivo*. With respect to gene expression, Applicants' cells would be reasonably expected to behave like the cells disclosed in the references. Accordingly, it is reasonably predictable that protein expression should continue to occur when Applicants' cell is in the animal.

Irrespective of the quote above, it is a well-accepted principle in the patent law that the specification need not disclose what is well-known in the art and *preferably omits* it. Hybritech states that a patent preferably omit what is well-known in the art. The amount of guidance and direction needed to enable the invention is inversely related to the amount of knowledge in the art as well as the predictability in the art. This is stated in the MPEP § 2164.03, citing In re Fisher, 427 F.2d 833 (CCPA 1970). The MPEP states "the more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification". In the instant case the references show that introduction of recombinant cells into an animal was widely and successfully used and could be done simply by obtaining protein expression in a cell *in vitro* and implanting that cell into an animal by any of the various well-known routes of introduction.

Further case law applies because Applicants' cells are reasonably predicted to be interchangeable, with respect to protein expression, with the cells of the references. The MPEP discusses In re Bundy, 642 F.2d 430 (CCPA 1981). The case held that if a composition is analogous to compositions known in the art, then even if the specification lacks examples of specific dosages, the claim is enabled because the compositions would be expected to behave the same way as the prior art compositions. Applicants believe that the instant case fits these facts. Applicants' cells are analogous to the recombinant cells in the references with respect to implantation and *in vivo* protein expression. Introduction of recombinant cells into animals and

subsequent protein expression *in vivo* was done in the art for up to almost twenty years prior to Applicants' disclosure. Applicants' cells should not be more difficult to introduce into an animal or less likely to express protein as the recombinant cells disclosed in the references. Since Applicants' cells can be used just as the cells in the art were used, the case law supports enablement of the method with Applicants' cells.

In addition to the issues raised above, on page 3 of the Office Action the Examiner also rejects the claims as not enabled because they recite only a transcriptional regulatory sequence but "the distinct feature of the vector taught in the instant application is that it comprises a splice donor site..." the specification does not teach that any vector comprising just a transcriptional regulatory sequence will function to overexpress or activate protein production from an endogenous gene. Applicants respectfully disagree.

The Application is broadly directed to introducing a *transcriptional regulatory sequence* into the genome of a cell to activate a gene. The following are examples.

> The invention is, therefore, generally directed to methods for overexpressing an endogenous in the cell, comprising and introducing a vector containing a transcriptional regulatory sequence into the cell, allowing the vector to integrate into the genome of the cell by nonhomologous recombination, and allowing overexpression of the endogenous gene in the cell.

Page 6, first paragraph.

> The invention is generally directed to methods for overexpressing an endogenous gene in the cell, comprising and introducing a vector containing a transcriptional regulatory sequence into the cell, allowing the vector to integrate into the genome of the cell by nonhomologous recombination, and allowing overexpression of the endogenous gene in the cell.

Page 35, second full paragraph.

The use of a splice donor sequence is not essential. The splice donor does not activate the gene. The transcriptional regulatory sequence activates the gene. The splice donor only comes into play when a gene has already been activated by the transcriptional regulatory sequence. The fact that splicing occurs is proof that there was activation by the transcriptional regulatory sequence in the first place.

In some instances the splice donor is superfluous. For example, to activate a single exon gene, there is no use for a splice donor sequence.

There is an advantage to adding a splice donor. Without a splice donor the transcriptional regulatory sequence has a more limited use. It is effective alone when it inserts

into an exon in the 5' untranslated region or into a downstream exon. When that happens the endogenous splice donors and splice acceptors form the final transcript. If, however, the transcriptional regulatory sequence integrated far upstream from the endogenous gene it could be hundreds of kilobases to the actual gene. This increases the likelihood that there will be cryptic starts of translation between the regulatory sequence and the gene. Accordingly, the use of a transcriptional regulatory sequence has some practical limitations when it comes to activating genes that are far downstream. The use of a splice donor obviates this problem by splicing over any of these cryptic signals. Accordingly, transcriptional regulatory sequences alone are useful, but they are more useful when they are operably linked with a splice donor.

In view of the above discussion and the amendments Applicants believe that the grounds for rejection have all been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

C. Double Patenting

On page 8 of the Office Action the rejection of claims on the basis of obviousness type double patenting has been maintained. Applicants traverse the rejection.

09/479,123 and 09/513,574 are abandoned. Claims 81, 83-88, 92, and 100-103 in 09/479,122 have been deleted or no longer depend on claims directed to *in vivo* expression. This is the case also for claim 88 of 09/481,375, claim 60 of 09/455,659, and claim 60 of 09/513,575.

Accordingly, Applicants submit that this rejection has been overcome. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

CONCLUSION

If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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